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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/058,546	04/10/1998	WALTER H. GUNZBURG	2316.1008-000	7592

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/058,546	GUNZBURG ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-16,18-21,23-27,29-31,33,36-55,58,59,61 and 63* is/are pending in the application.

4a) Of the above claim(s) *5-7,12,18,24,25,29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9-11,13-16,19-21,23,26,27,31,33,36-55,58,59,61 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9-15-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9-15-04 has been entered.

Claims 8, 17, 22, 28, 32, 34, 35, 56, 57, 60, 62 and 64 have been cancelled. Claims 1-7, 9-16, 18-21, 23-27, 29-31, 33, 36-55, 58, 59, 61 and 63 remain pending.

Applicant's arguments filed 9-15-04 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The application on pg 12, lines 26-27, has been corrected.

Information Disclosure Statement

The IDS filed 9-15-04 has been entered. An initialed copy of the PTO-1449 is attached herewith.

Election/Restriction

This application contains claims 5-7, 12, 18, 24, 25, 29 and 30 drawn to an invention nonelected with traverse in Paper No. 17. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP ' 821.01. Applicants basically argue that claims 1-4, 9-11 33-38, 44, 49, 54 and 55 require retroviral vectors and retroviral particles made for the ultimate purpose of producing retroviral particles that make SDI-1 and not SDI-1 antisense. Applicant argue a DNA "strand that is 'encoding' a polypeptide is the sense strand, even though the patent office is correct that the non-coding strands is the one that is used for mRNA transcription, and that this strand is typically regarded as the antisense strand." Applicants' argument is unclear but upon further consideration, Groups I and II have been recombined in part.

Claims 1-4, 9-11, 33-38, 44, 49, 54 and 55 require a retroviral particle having RNA that encodes SDI-1. A retroviral particle comprises RNA and is used to transduce the target cell; the retroviral particle has RNA encoding SDI-1. Therefore, claims 1-4, 9-11, 33-38, 44, 49, 54 and 55 have been recombined with claims 13-16, 19-21, 23, 26, 27, 31, 39-43, 45-48, 50-53, 58, 59, 61 and 63 because they relate to the production of retroviral particles that make SDI-1 and not SDI-1 antisense.

Claim 5 requires "a DNA sequences which is antisense to the SDI-1 gene" which appears to require the production of SDI-1 antisense, which is contrary to the parent

claim. Claim 5 is distinguished from claim 2, which merely requires the retroviral vector comprises a DNA sequence encoding SDI-1. A retroviral vector is DNA and is used to transfect the packaging cell; the retroviral vector has the antisense DNA encoding SDI-1. "Antisense DNA" is the strand of DNA complementary to the one bearing the genetic message and can be used as a potential therapeutic to stop transcription or translation (see definition of antisense DNA from Stedman's Medical Dictionary attached). Claims 5-7, 12, 18, 24, 25, 29 and 30 are confusing but appear to be attempting to limit the claims to the production of SDI-1 antisense. Therefore, claims 5-7, 12, 18, 24, 25, 29 and 30 remain withdrawn because they appear to relate to Group II, which relates to the production of SDI-1 antisense.

Claims 1-4, 9-11, 13-16, 19-21, 23, 26, 27, 31, 33, 36-55, 58, 59, 61 and 63 are under consideration in the instant office action.

Claim Objections

The objection to the term "harbouring" throughout the claims has been withdrawn because the term has been changed to –comprising--.

The objection to claims 15, 41, 46, 51 and 56 has been withdrawn. Claims 15, 41, 46 and 51 have been clarified as suggested by the examiner and claim 56 has been canceled).

The objection to claim 63 has been withdrawn because the claim has been amended as suggested by the examiner.

Claim 1 is objected to because the preamble does not correlate to the rest of the claim and because it includes extraneous information. Claim 1 is drawn to a method of producing a recombinant retroviral particle. The method should have steps that result in the production of a retroviral particle, but instead only requires stably transfecting an isolated producer cell line, e.g. 1) stably transfecting an isolated producer cell line with a retroviral vector... ; 2) producing retroviral particles from the producer cell line or stably transfecting an isolated producer cell line with a retroviral vector such that retroviral particles encoding an SDI-1 polypeptide or a functional fragment thereof are produced.

The phrase "encoding an SEI-1 polypeptide or a functional fragment thereof" in the preamble of claims 1, 13, et al. should parallel the description of the retroviral vector in item b which currently only requires an SDI-1 coding sequence.

The phrase "said SDI-1 polypeptide or functional fragment thereof inhibits cell proliferation" in claims 1, 13, et al., (i) should be with the description of the sequence encoding an SDI-1 polypeptide or a functional fragment thereof" in (b).

The phrase "isolated producer cells line" in claim 14, line 2, is objected to for improper tense.

The preamble of claim 21 is objected to because it uses awkward syntax and is not concise. The phrase "treating an individual having a tumor or restenosis" is more concise.

Claims 21, 27, 31, 59 and 63 are objected to because the phrase "administering to the individual at a site of the tumor or the restenosis the capsule of claim 15" (for example) can be written more clearly to describe the method of administration. The phrase uses awkward syntax and the phrase "at a site of the tumor" is less than clear because while a patient may have a tumor site, a tumor does not really have a site as claimed. "A method of treating a patient having a tumor or restenosis comprising administering a retroviral particle into the tumor or the site of restenosis of said patient" is clear.

Claim 63 is missing "or restenosis" after line 2 before "a capsule".

Claim Rejections - 35 USC ' 112

I. Claims 1-4, 9-11, 13-16, 19-21, 23, 26, 27, 31, 33, 36-55, 58, 59, 61 and 63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amendments to the claims are new matter.

No support for the phrase "in 5' to 3' order", "wherein into said deleted U3 region has been cloned a polylinker sequence into which a regulatory element or a promoter has been inserted" or <after infection of a target cell... ...SDI-1 coding sequence in said target cell" in claims 1, 13, 33, 39, 45 and 50 has not been provided and none can be found.

The phrase "at a site of the tumor or restenosis" in claims 21, 31, 59 and 63 is new matter. No support for the phrase has been provided and none can be found.

The phrase "Whey Acidic protein... ...regulatory elements" in claim 37 is new matter. No support for the phrase has been provided and none can be found.

II. Claims 15, 16, 20, 21, 23, 27, 31, 32, 41, 42, 46, 47, 51, 52, 56-59, 61 and 63 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating restenosis or cancer by contacting the site of restenosis or cancer with a retrovirus encoding SDI-1 resulting in a therapeutic effect, does not reasonably provide enablement for using any mode of delivery as broadly claimed, using producer cells or capsules that make retroviral vectors encoding SDI-1 to treat disease, or using retroviral vectors encoding fragments of SDI-1 to treat disease. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The rejection regarding claims 21, 23, 27, 31, 59, 61 and 63 and the route of administration has been withdrawn in view of the amendments adding the language to the claims.

Claims 15, 16, 20, 21, 23, 41, 42, 46, 47, 51, 52, 58, 59, 61 and 63 encompass capsules comprising producer cells that make retroviral particles encoding SDI-1, and methods of treating tumors or restenosis using the capsules. The only disclosed use in the specification for the capsules claimed are for therapy *in vivo*. Applicants have not pointed to another purpose for the capsule. The rejection regarding using capsules for therapy is maintained.

The specification does not provide adequate guidance to use capsules comprising producer cells that make a retrovirus encoding SDI-1 to treat tumors or restenosis. The mode of delivery required to obtain a therapeutic effect using retroviral vector gene therapy was unpredictable at the time of filing for reasons of record.

The art at the time of filing taught how to use retroviral particles to treat tumors or restenosis but did not teach how to administer encapsulated producer cells making the retrovirus to obtain an equivalent effect. While retroviral gene therapy was known in the art, no one had used encapsulated producer cells making a retrovirus to obtain a therapeutic effect or determined whether encapsulated producer cells produced

therapeutic levels of retroviral particles *in vivo* such that a therapeutic effect could be obtained. Therefore, the art of using encapsulated producer cells that made retroviral particles for therapy was unpredictable.

The specification does not teach the amount of retroviral particles secreted from the capsule, the amount of retroviral producer cells required to obtain therapeutic levels of retroviral particles or how to obtain therapeutic levels of retroviral secretion from the producer cells and capsule *in vivo*. Retroviral particles known to have a therapeutic effect were concentrated during preparation *in vitro*; only preparations with adequate titers of infectivity were used. The specification does not provide adequate guidance indicating the producer cells in the capsules would secrete the same amount of retroviral particles as the retroviral stock concentrated *in vitro*. The specification does not teach the titer of the retroviral particles produced in the capsule was the same as the retroviral stock selected for its high titer *in vitro*.

Given the unpredictability in the art, the absence of using capsules comprising retroviral producer cells to treat disease, and the guidance provided in the specification about how to administer a capsule comprising retroviral producer cells to treat disease, it would have required one of skill undue experimentation to determine how to administer capsules comprising retroviral producer cells to treat disease.

Applicants argue US Patent 6,776,985 enables the invention because it taught an example of obtaining tumor regression using a capsule comprising producer cells

that made retroviral particles encoding rat cytochrome p450 2B1. Applicants' argument is not persuasive. '985 taught administering capsule producer cells at the site of a tumor, but '985 was not available to the public until it was published in August of 2004; therefore, '985 cannot be relied upon for enablement of what was known in the art. '985 was filed by applicants before the instant application; however, the instant application does not contemplate using the capsules *in vivo*. Thus, applicants knew capsules could be administered to a tumor site but excluded such embodiments from the instant application. Therefore, it is not readily apparent that the instant invention encompassed using capsules to treat disease because such embodiments were excluded from the instant application. In addition, the instant application relates to a retroviral vector encoding SDI-1 while '985 relates to a retroviral vector encoding cytochrome p450.

The rejection regarding "functional fragments" of SDI-1, specifically amino acids 1-71 of SDI-1, that provide a therapeutic effect has been withdrawn. Pg 8,lines 20-25, describe amino acids 1-71 of the SDI-1 as having essentially the same effect as full length SDI-1.

Claims 15, 46, 47, 51, 52 and 63 remain rejected for reasons of record regarding using amino acids 42-58 of SDI-1 to treat disease. Claims 4, 49-53, 58, 59 and 61 encompass capsules comprising packaging cell lines that make retroviral particles encoding amino acids 42-58 of SDI-1. The specification and the art at the time of filing did not teach that amino acids 42-58 of SDI-1 had the same function as full length SDI-1

or had any inhibitory effect *in vivo*. Applicants have not addressed this portion of the rejection.

III. Claims 13-16, 19-21, 23, 26, 27, 31, 32, 39-43, 45-48, 50-53, 59, 61 and 63 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "a 5' LTR region of the structure U3-R-U5" (13, 39, 45, 50) is unclear. A 5' LTR having such a structure cannot be determined. One of skill would not know when the phrase had been met. It cannot be determined how much of the U3, R or U5 region is required to have the structure of a U3, R or U5 region.

Applicants argue one of skill would recognize the phrase and be able to determine when a 5' LTR had a U3, R and U5 region. Applicants' argument is not persuasive. Those of skill in the art readily knew that the U3, R and U5 regions of a retroviral 5' LTR could be mutagenized in the lab. Those of skill would not know the metes and bounds of when a mutated U3, R or U5 region still had the "structure" of a U3, R or U5 region. For example, if all but the last 5 nucleotides of a U5 region are deleted, it is unclear if the remaining 5 nucleotides of the U5 region constitute a U5 region. As such, one of skill would not be able to determine if they were infringing on a claim that required the 5' LTR had a U5 region. If all but the last 2 nucleotides the U5

region are deleted, are those of skill infringing on the claim? It cannot be determine where to drawn the line between nucleic acid sequences that do and do not have the structure of a U3, R and U5 region. The metes and bounds of the elements making up the 5' LTR are unclear thus making the metes and bounds of a "5' LTR region of the structure U3-R-U5" are unclear.

The rejection regarding the phrase "one or more sequences selected from coding and coding and noncoding sequences" in claims 13, 15, 39, 45 and 50 has been withdrawn in view of the amendment.

The rejection regarding a U3 region with a partial or complete deletion has been withdrawn. The structure of a U3 region in a 3' LTR was known in the art; therefore, one of skill could determine when a 3' LTR had a complete or partial deletion of the U3 region.

The phrase "wherein into said deleted U3 region has been cloned a polylinker sequence into which a regulatory element or a promoter has been inserted" in claims 1, 13, 15, 39, 45 and 50 (and elsewhere) as newly amended is unclear. The metes and bounds of sequences encompassed by the phrase "polylinker sequence" cannot be determined because "polylinkers" usually refer to oligonucleotides that provide a restriction site. It cannot be determined if the polylinkers have restrictions sites and a regulatory element/promoter or if the polylinkers are a regulatory element/promoter. Secondly, he phrase is confusing because it uses improper syntax. Finally, the phrase

is indefinite because a polylinker inserted into the deleted U3 region as claimed would not be part of the retroviral vector because a polylinker inserted into a deleted U3 region would also be deleted.

The phrase "after infection of a target cell... ...said SDI-1 coding sequence in said target cell" in claim 1 and elsewhere is indefinite. It is unclear if the phrase is describing a function of the retrovirus or a step in the method, i.e. infecting a target cell. The phrase "replaced by said completely or partially deleted U3 region" does not make sense because the deleted U3 region is gone and cannot replace anything. If the phrase is describing the function of the "3' LTR" of (c), the phrase should be with (c). The phrase "resulting in said SDI-1 coding sequence becoming" should parallel the language used throughout the claim and include "fragments thereof".

The rejection regarding the phrase "said SDI-1 sequence encoding a polypeptide with SDI-1 activity of inhibiting cell proliferation" in claims 13, 15, 39, 45 and 50 has been withdrawn in view of the amendment.

The rejection regarding the phrase "a polypeptide with SDI-1 activity of inhibiting cell proliferation and being under transcriptional control of said regulatory element or promoter" in claims 13, 15, 39, 45 and 50 has been withdrawn in view of the amendment.

The rejection of claim 15 regarding whether the capsule comprises the isolated producer cell or if it is simply capable of comprising the producer cell has been withdrawn in view of the amendment.

The rejection of claims 21, 27, 31, 59 and 63 regarding the phrase "the site of the tumor" lacks antecedent basis in parent claims has been withdrawn because the parent claims require the individual has a tumor as newly amended.

The rejection regarding the phrase "the living animal body" lacking antecedent basis in claim 63 has been withdrawn because the phrase has been deleted.

The rejection regarding the phrase "living animal body, including a human, in need thereof" in claim 27, 31 and 63 has been withdrawn because the phrase has been deleted.

The rejection regarding claim 32 has been withdrawn because the claim has been canceled.

The rejection of claim 63 has been withdrawn because the claim has been amended.

The phrase "said recombinant retroviral particle" in claim 13, (ii), lacks antecedent basis.

Claim Rejections - 35 USC ' 103

The rejection of the claims under 35 U.S.C. 103(a) as being unpatentable over Miller (1989, Biotechniques, Vol. 7, pages 980-990) or Price (1987, PNAS, USA, Vol. 84, pages 156-160) in view of Nabel (US Patent 5,863,904, Jan 26, 1999) has been withdrawn because the Miller, Price and Nabel did not teach the retroviral vector with a deletion in the 3' LTR U3 region, wherein a promoter or regulatory element is inserted into the deletion as claimed.

The rejection of the claims under 35 U.S.C. 103(a) as being unpatentable over Gunzburg (WO 9607748, March 14, 1996) in view of Nabel (US Patent 5,863,904, Jan 26, 1999) has been withdrawn because Gunzburg (published March 14, 1996) is not prior art in this application which has priority to Denmark patent application DK0740/95 filed June 27, 1995.

The claims are free of the prior art because the prior art did not teach or suggest a retroviral vector with a deletion in the 3' LTR U3 region, wherein a promoter or regulatory element is inserted into the deletion as claimed.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the

office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER